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Letters to the Editor

Hydatidiform moles

Dear Sir

We would like to report on eight cases of complete hydatidiform moles in a sibship of six women aged 16–35 years. No child has been born yet to any of these women. All pregnancies have had to be terminated due to hydatidiform moles diagnosed by ultrasound scan. The pedigree of the family concerned is given in Figure 1.

Dizygotic twin sisters, B and C, came to our genetic counselling unit after having had two complete hydatidiform molar pregnancies each. The recurrence risk was assumed to be high, without knowing exactly where it had to be settled. Then C suffered from two further molar pregnancies, fortunately the elevated chorionic gonadotrophin levels fell rapidly into the normal range.

Subsequently a third sister, E, had two pregnancies which had to be terminated due to the same trophoblast disorder. D never became pregnant. In spite of infertility treatment for several years—in-vitro fertilization had not been performed—no pregnancy could be achieved.

The genetic counsellor was asked whether any possibility existed of having a normal pregnancy in this family. The causative mechanism for the frequent occurrence of hydatidiform moles in this female sibship is not known. Where did mutations occur—were they dominant? maternally inherited? How do they affect further pregnancies? Unfortunately we have not succeeded in obtaining molar tissues to perform cytogenetics, DNA analysis or fluorescence in-situ hybridization.

We would like to receive information about similar cases of familial hydatidiform moles.

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Dear Sir

It is one of my regrets that several sibships such as that described by Drs Kircheisen and Ried have not presented at IVF clinics where I have worked. Repeated hydatidiform mole is a major problem in these couples, with an increasing likelihood of occurrence for each successive molar pregnancy. To the best of my knowledge, there is no treatment for the condition, yet assisted conception could help to unravel its causes and perhaps one day help to alleviate it.

A single couple did present to us, and the successive details of fertilization, syngamy and cleavage were examined in detail (Edwards *et al.*, 1990, 1992). The analyses revealed an astonishing set of circumstances in their fertilized eggs, quite outside my experience of human fertilization *in vitro*. Among 11 eggs with pronuclei, only one had two normal-looking pronuclei, and several others showed anomalies such as a single pronucleus, a delayed-appearing pronucleus, three pronuclei with two of them in close apposition as if joined by the spindle mid-body, and 'immediate cleavage'. We interpreted these events as being due to malformations in spindle mechanics as the second polar body was extruded, so that all maternal chromosomes could be expelled or retained, or the spindle body could move entire into the centre of the egg before being activated (immediate cleavage).

The eggs with two pronuclei cleaved into embryos that appeared in general to be normal, but failed to survive cryopreservation; an unusual event since the freezing programme was highly successful when this work was done. Those eggs with a single pronucleus had two polar bodies, and they displayed an astonishing performance at syngamy. Judged from their pronuclear and syngamic histories, the single pronucleus condensed to form a unipolar spindle, then reformed a somatic nucleus and later apparently formed a normal bipolar spindle since each of them cleaved to normal 2-cell embryos, and continued to divide. We interpreted these events as resulting in androgenic diploid embryos.

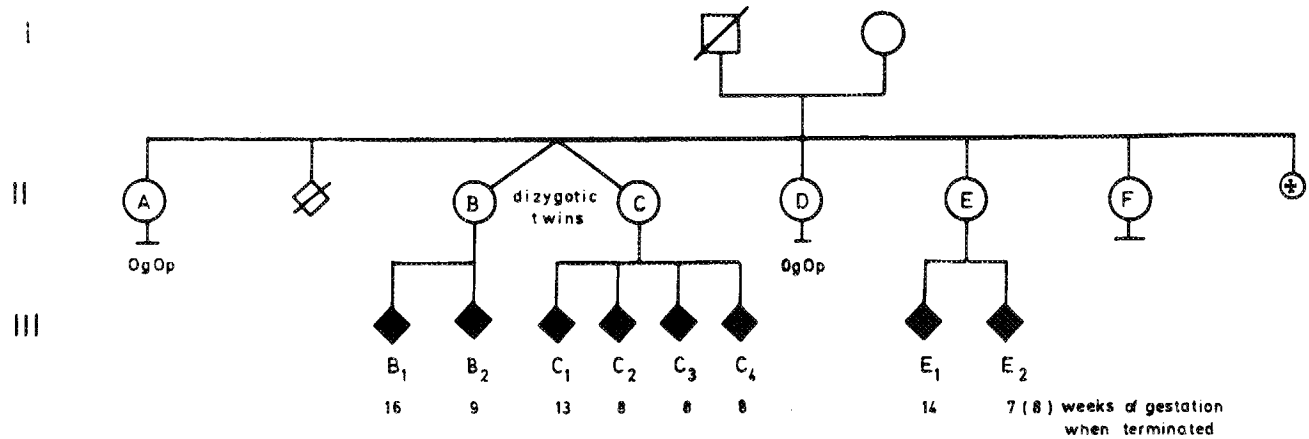

Fig. 1. Pedigree of the family.

This astonishing compilation of anomalies in a single case of repeated hydatidiform mole could obviously seriously preclude normal fertilization and development. It could lead to long-standing infertility, in addition to producing androgenic diploids and other anomalies. To our regret, the patient did not return for further treatment, so it was impossible to carry out any further embryological or genetic analyses on the eggs and embryos. Nevertheless, the groundwork was laid for a theory on the origin of these disorders, which must include anomalies in the cell-cycle factors regulating the orientation and induction of the second meiotic division and extrusion of the second polar body. The events at syngamy must also involve the sperm centriole, as outlined in classical experiments in echinoderm and other species, and now suspected to be involved in such events at syngamy during fertilization in mice (Edwards, 1958; Edwards and Sirlin, 1959) and man (Palermo *et al.*, 1994).

It is just possible that the anomalies arising during fertilization in the eggs of patients with recurrent hydatidiform mole could be corrected by modern IVF technology. Detailed analyses are needed on such sibships, with an eye to clarifying our observations. If these are confirmed, it may be possible to apply methods of pronuclear excision or transfer, that is to restore a normal male and female pronucleus to the fertilized eggs. This would be exciting, in that some form of surgical correction would, for the first time, be applied to an embryo which would otherwise become abnormal. I hope that Drs Kircheisen and Ried will be able to undertake such analyses on the sibship they have described.

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Trend in legitimate and illegitimate multiple births

Dear Sir,

From the middle of this century to late 1970s the frequency of (dizygotic) multiple births has constantly declined in most countries. In the early 1980s, however, it levelled off and in the mid-1980s started to rise in most countries (Elwood, 1983; Parazzini *et al.*, 1991). This finding, with the increasing trend of frequency of triplets, has essentially been interpreted in terms of consequences of the treatment for infertility (Editorial, 1989). The 'true' trend of multiple pregnancy rates in the absence of treatment for infertility is unknown. To offer some indirect data on the issue, we analysed the trends of multiple births in Italy in legitimate and illegitimate births, assuming that assisted reproduction is rare in illegitimate births.

Numbers of single and multiple births according to maternal age and legitimate or illegitimate status for the period 1960–1989 were obtained from annual publications of the Central Institute of Statistics (ISTAT, 1989). Illegitimate births represented about 2% of births in Italy in 1960 and 6% in 1989.

Table I shows the multiple birth rates for selected calendar years in legitimate and illegitimate births. Multiple births in legitimate births declined until 1980, but increased thereafter, being 12.0/1000 births in 1960, 9.3/1000 births in 1980 and 10.7/1000 births in 1989. Multiple birth rates in illegitimate births tended to be slightly higher than in legitimate births from 1960 to 1985 (being 12.6/1000 births in 1960 and 9.9/1000 births in 1985), but in 1989 continued to decline and occurred at a rate of 9.1/1000 births (95% confidence interval 8.1–10.2). These trends in multiple illegitimate birth rates are not substantially affected by standardization for maternal age (data not shown).

These findings suggest that, in the absence of treatment for fertility, the declining trends of multiple birth rate would have continued until the late 1980s. As a first approximation, it is possible to estimate that in Italy ~500–600 multiple births each year were attributable to the treatments for infertility in the late 1980s.

Table I. Trends in multiple birth rates in legitimate and illegitimate births in Italy, 1960–1989

Calendar year	Rate/1000 births	
	Legitimate	Illegitimate
1960	12.0	12.6
1965	11.3	10.4
1970	10.3	10.9
1975	9.7	10.5
1980	9.3	9.8
1985	9.4	9.9
1989	10.7	9.1

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